THE BRADSHAW LECTURE
ON
Prognosis in Relation to Disease
of the
Nervous System

JUDSON S. BURY, M.D.Lond., F.R.C.P.

With the Lecturer's compliments

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22nd August, 1906

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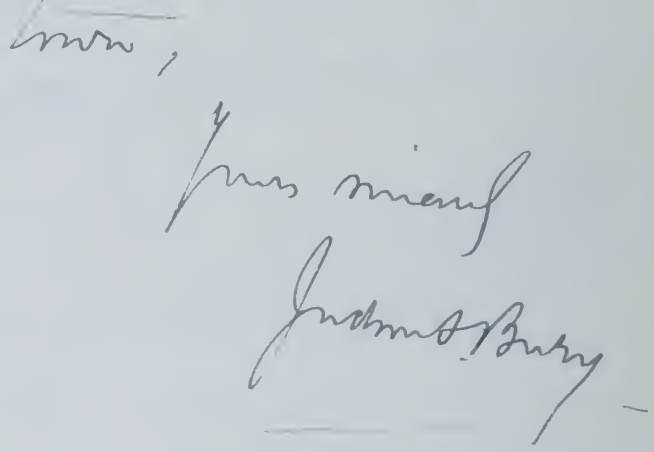

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Delivered before the Royal College of Physicians of London, November 5th, 1901.

By Judson S. Bury, M.D.Lond., F.R.C.P.,
Physician to the Manchester Royal Infirmary.

Mr. President,—Allow me to thank you for the great honour you have conferred upon me by asking me to deliver the Bradshaw Lecture this year, and to express a wish that the value of my lecture were in any degree equal to my appreciation of the honour.

When we first enter upon the practice of medicine we are, perhaps, too apt to separate diseases from a prognostic point of view into the curable and the incurable, that is, to recognise one class of diseases in which complete recovery is the rule, and another class in which the tendency is to a fatal issue or to only partial recovery. With increasing experience of the course and terminations of morbid processes, we find ourselves less able to draw sharp distinctions between the ultimate results of different diseases. We meet with formidable disease which appears to have been caused by some simple ailment that we had regarded as being completely cured. For example, we attend an adult suffering from influenza. In a fortnight he appears to be quite well, but a year later he consults us for headache, nervousness, incapacity for work, and other symptoms which constitute the condition known as neurasthenia, and he says that he has never been the same man since the attack of influenza. On the other hand, if we study diseases that are regarded as incurable, we are surprised to find that every now and then such a disease is apparently completely cured. Thus

we occasionally see cases which present the classical symptoms of brain tumour in which, after a time of anxiety, a stationary stage is reached; the prognosis becomes more hopeful, and, as regards the prospect of mere existence, it may be very good. More rarely we see a child recover from symptoms which, rightly or wrongly, we regarded as indications of tuberculous meningitis.

Such experiences tend to make us more cautious regarding the prognosis of ailments which usually recover, more open-minded in respect to those which, as a rule, pursue a downward path. We begin to believe (1) that illness, however slight, may leave behind it some weak spot which, after months or even years, may be attacked by a noxious agent and become the starting-point of chronic progressive disease; and (2) that severe organic disease is not always fatal; that sometimes the morbid process is arrested, and, in exceptional cases, even completely cured. A full consideration of the subject, indeed, shows us that an accurate prognosis of disease is well nigh impossible, and that even an approximate forecast presents great difficulties which are perhaps more prominent in relation to diseases of the nervous system than to diseases affecting other parts of the body.

The problem before us may be stated as follows:—A part of the nervous system—say, a nerve cell—is attacked by a poison. The effect will depend partly upon the nature, the virulence, and the duration of the action of the poison, and partly upon the resistance offered by the cell. Both factors present infinite variations. If we think only of the resistance of the cell which depends on its condition at the time of attack, we see that this condition is the result of all the influences that have been brought to bear on the cell during its birth, development, and existence—that is, of its inherited qualities, and its environment past and present. Moreover, its resistance may be helped by agencies outside it; for example, the development of antitoxins. It may be lowered, owing to the cell being cut off, in consequence of its altered condition, from the full benefit of the sensory and

other impulses which it normally receives from adjacent neurons. The resistance, too, may be modified by influences which the lesion has itself induced in other parts of the nervous system; as, for example, the inhibition of the functions of other centres. Furthermore, the direct effect of the changed condition of the cell on its surroundings, as on its axon or on the arborisations of neighbouring neurons, has to be taken into account before we can attempt to grasp the pathology of the situation. The results of such cell disturbance are manifested to our senses by what we call symptoms, and very often they are the only elements of the disease with which we are acquainted. Thus the condition known as hysteria is a mere collection of symptoms, which may give us information as to the site, but none as to the nature, of the lesion. In other cases we know something of the attacking agent—as, for example, syphilis—and of the changes it produces in nerve tissue, and then we can form a more complete diagnosis. But even in these cases it is usually far easier to make a regional than a pathological diagnosis; and this will continue to be the case until our knowledge of the causes of disease has attained a firmer basis. It is, then, our ignorance of etiology and of general pathology in its broadest meaning which makes our diagnosis and our prognosis so often imperfect or erroneous. In the meantime, it may be profitable to review our knowledge of some of the elements which, as I have indicated, are essential factors in the framing of a prognosis.

Prognosis in Relation to the Attacking Agent.

Our knowledge of the various agents that may set up disease is too limited to help us much in making a forecast of particular ailments. A clot in a cerebral vessel will rob a portion of brain of its blood supply, and thus lead to impairment or loss of functions, but from the symptoms presented to us we cannot determine whether the obstruction will be temporary or permanent. A blow on the head, insufficient in force to cause fracture of the skull or other gross lesion, may produce symptoms

of concussion from which the patient slowly recovers, but we are unable to say that a cure is established, for a train of symptoms may begin to develop some time after the accident, symptoms which in some cases indicate a more or less permanent damage to cortical cells; while in other cases they point to the presence of a brain tumour.

There is good evidence that irritation of sensory nerve fibres may lead to muscular atrophy. Thus articular lesions are often quickly followed by wasting of the muscles that move the affected joint, and especially of its extensor muscles. In some cases the atrophy is persistent, and it may spread to other muscles of the limb. I believe that sometimes progressive muscular atrophy is initiated in a similar manner. For example, a policeman in a severe struggle with a maniacal patient strained some of the muscles of the right arm. Two or three weeks later he noticed that the limb was getting thin and weak, and in a few months the case was clearly one of chronic anterior poliomyelitis.

An absence of the secretion of the thyroid gland appears to be the cause of the impaired brain functions met with in cretinism and in myxœdema, while absence of the parathyroid secretion has probably something to do with the origin of exophthalmic goître; still we know but little regarding the resulting chemical changes which lead up to these diseases, nor can we say how far symptoms in other nervous maladies may depend on modifications in the quantity or the quality of gland secretions which enter the circulation. As to poisons which may be regarded as the commonest causes of nervous disease, we are daily acquiring more knowledge. We know a good deal regarding the course of diseases produced by alcohol, lead, arsenic, and other poisons which are introduced into the body, and something of the effects caused by poisons which are the products of bacteria, and which are produced within the body, such as the toxins of syphilis and tubercle. By analogy rather than by actual demonstration the nervous sequelæ of specific infectious diseases are attributed to the effects of the toxins of special micro-organisms.

In the case of disseminated sclerosis, infantile paralysis, myelitis, and many other nervous affections, we assume that they, too, may be set up by poisons, some of which might be derived from the products of over-fatigue or of abnormal digestion in the alimentary canal, or from the perverted function of some other organ or tissue.

Two striking features may be noted regarding the effects of poisons—namely, their selective action and the immunity which is the direct result of their action. Immunity, however, is not known to occur in the case of poisons which are not of bacterial origin, with the exception of opium and tobacco. In the case of toxins, both selective action and immunity play an important part in the prognosis of disease, and may now be briefly illustrated by reference to the nervous diseases produced by syphilis. The poison of syphilis shows a preference for the vascular structures at the base of the brain, for branches of the cerebral and spinal vessels, for the afferent conducting paths of the spinal cord, and for the cortical cells in the anterior part of the brain.

Now it is often stated that organic affections of the nervous system run a more favourable course when due to syphilis than when they are started by other agencies. The statement, if true, must be taken with considerable qualifications. When brain tissue is destroyed by the blocking of an artery, it matters not whether the clot be of syphilitic or other origin; the result is permanent impairment of function. If brain tissue is damaged but not destroyed, then as much recovery may take place when the arterial obstruction is due to embolism from heart disease as when it is due to thrombosis from syphilitic endarteritis. But if there is only a narrowing of vessels, there is reason to believe that the thickening is more amenable to treatment if syphilitic than if due to other forms of arterial sclerosis.

Exudation from syphilitic vessels may be removed by treatment, but it is impossible to say to what extent this will occur in any individual case. Moreover, there can be no doubt that absorption of exudations occurs in other specific infections, as,

for example, in connection with the inflammatory products which sometimes occur in the brain as a result of influenza, or in the cord in cases of myelitis of unknown toxic origin, for it is certain that occasionally well-marked symptoms of myelitis not due to syphilis entirely pass away. Two marked instances of such recovery have recently been under my care.

Even if it be admitted that syphilitic exudations are more readily removed than those which are not syphilitic, the admission is not opposed to a further statement—namely, that the prognosis of syphilis in relation to nervous diseases may, in respect to the final outcome, be worse than that of any other poison. One thing at least is certain—the germs of syphilis once introduced into the body are difficult to destroy.

A syphilitic patient recovering from an attack of right hemiplegia may be seized with left hemiplegia. A syphilitic myelitis may develop some years after symptoms of cerebral syphilis, or a patient suffering from syphilitic meningo-myelitis may make a partial or complete recovery, and be adequately treated for a long time afterwards, and yet subsequently may have another serious breakdown in some part of his nervous system. In this respect syphilis presents a contrast to the acute specific fevers. For example, if the poison of measles sets up a disseminated myelitis and the patient recovers, we are pretty confident that no subsequent nervous affection will develop as a result of the original infection. In syphilis, on the contrary, there appears to be an infinite capacity for future developments of its toxins. Some authorities have stated that if a person who has contracted syphilis is placed under proper treatment for a couple of years he may in the majority of cases be regarded as completely cured. My experience is opposed to such an opinion. It may be true that some persons are cured, but we cannot anticipate such a result. It does not follow because a person presents no symptoms for many years that he is cured. The germs of syphilis may lie hidden in his body, giving not the slightest indication of their deadly presence; and then, after a period of ten or even twenty

years, may suddenly revive, shatter his nervous system, and put an end to his life, after a few years of insanity or of a painful, miserable existence. If this be the outlook for the future condition of the nervous system in the subjects of acquired syphilis, what is to be said of the prognosis when the poison is inherited? Here the outlook is equally uncertain, and if possible even more gloomy, for the type of nervous syphilis in the child is a diffuse sclerosis of the cerebral cortex which arrests its growth, paralyses its highest functions, and slowly but surely leads to chronic progressive dementia.

Now, if we have to speak so cautiously about the course of diseases produced by a poison, the effects of which have been so carefully studied as those of syphilis, how much more caution is necessary in speaking of the action of poisons whose effects are so little known as those which we assume to be the exciting agents of disseminated sclerosis, of Landry's paralysis, and of many other forms of nervous disease?

At the outset I alluded to influences, inhibitory or otherwise, which tend to modify the resistance of the part first attacked by an injurious agent. A consideration of such influences is of great interest, but I must pass them by in order to have time to make some remarks on the relation of prognosis to the changes which are the result of these counteracting forces, and to their outward expression by means of symptoms.

Prognosis in Relation to Morbid Anatomy.

To what extent is the course of a nervous disease modified by the size, situation, and nature of the lesion present?

Size of Lesion.

The mere size of a lesion appears to have but little influence on the progress of disease. A slowly-growing tumour in certain regions of the brain may reach a large size without giving rise to much disturbance of function; moreover, its development may be arrested, all the symptoms produced by it may pass away,

and occasionally a partial recovery is established. On the other hand, a person who presents the group of symptoms which constitute Landry's paralysis, or the condition known as myasthenia gravis, may die within a few weeks or months and no changes be found in the nervous system after the most careful microscopical examination. The terms "functional" and "organic" have been somewhat unfortunately used to separate diseases according to the presence or absence of visible changes. Now, visibility is a relative term; it depends on our eyesight and the powers of our microscopes, and, as regards nervous structures, to some extent on staining reagents, and, let it not be forgotten, on the thoroughness of our search. Hence with improved methods of investigating nerve tissue, we may expect that the group of functional disorders will get smaller and smaller. If on grounds of convenience these terms be retained, two points should be clearly recognised, namely: (1) The term "functional" ought to mean, not the absence of morbid changes, but only the absence of detectable changes; and (2) it ought not to be taken for granted that a disorder which has no known structural changes will run a more favourable course than one in which such changes are apparent.

The lesions underlying paralysis agitans, exophthalmic goître, epilepsy, and spasmodic torticollis are unknown to us, yet we cannot regard these diseases as curable. Death may result from a profound chemical disturbance of the atoms and molecules of nerve tissue which leaves no visible trace, and between such minute changes and a large lesion there must be every gradation in size.

Situation.

When the bulbar neurons which preside over the functions of respiration and deglutition are involved, life is seriously endangered. When other cells and fibres are implicated, the question of loss of function has to be considered rather than that of any immediate danger to life. It may be accepted as a general

law that, other things being equal, lesions of the peripheral nerves are more quickly and completely recovered from than lesions of the central nervous system, and that lesions of the brain, at least as regards the degree to which function is impaired, are less serious than those of the cord. Thus the brain may be the seat of relatively large lesions without any definite symptoms being produced, while, owing to the small space transversely occupied by the centres and conducting paths in the cord, a comparatively slight lesion may injure it irretrievably.

The situation of the lesion influences the degree to which impaired or lost function may be compensated for by the action of healthy parts of the nervous system, and, therefore, it has a definite relation to prognosis. For example, in hemiplegia the motor power of the leg is more readily restored than that of the arm, because the motor neurons of the legs are more intimately connected by association fibres in the cerebral and spinal commissural tracts than are those of the arm. In infantile paralysis the functions of the cells in the anterior horns, which are destroyed at a certain level, may be taken up by healthy cells at a higher or lower level. The principle of compensation also may be seen in cases of muscular atrophy, where a muscle may hypertrophy in fulfilling the function of its atrophic neighbour. It explains also to some extent the more favourable prognosis in affections of the sensory, as compared with those of the motor, mechanism, for, as is well known, the conduction of motor impulses is much more restricted to definite tracts than is that of sensory impulses.

As regards the central nervous system then, restoration of function may be said to be due either to the recovery of nerve tissue which is only partially damaged, or to the taking up by adjacent or distant structures of the functions that are lost, for there is no satisfactory evidence, and I have Dr. Mott's authority in support of the statement, that nerve cells or fibres in the brain or cord which are completely destroyed, can ever be replaced by new cells or fibres. Dr. Mott informs me that he has fre-

quently, in degenerating tissue, seen attempts at mitosis of the nucleus of a cell, but he has never seen this proceed to the development of a new cell.

With regard to the pathological significance of lesions in different parts of a nerve cell the observations of Marinesco, Lugaro, and other investigators, are of great interest. Lugaro[1] states that "lesions of the chromatic part are the first to appear in all cases in which the harmful action does not act suddenly and with such energy as to paralyse function; that they are in every case reparable, even when very grave, provided that the other parts of the cell have not suffered serious damage. It is very doubtful, however, if lesions of the achromatic part can be repaired, more especially since they very often appear contemporaneously with lesions of the nucleus, the integrity of which is indispensable for the conservation of the cell. He points out that there is no exact and constant relation between lesions of the chromatic part and functional disturbance, that the functional activity of the cell can continue even when the chromatic part is injured, and that this part does not possess structural arrangements necessary for the fulfilment of its function, which depends therefore upon chemical composition, and not upon morphological disposition. Within certain limits of structural alteration function can remain intact, and will not exhibit disturbance with certainty except in cases of grave alteration, when the nutritive alteration is also grave. On the other hand, function will be entirely suppressed when the structural dispositions of the achromatic part, which seem more strictly related to the nervous conduction, are altered, or when they are suddenly affected by energetic chemical action."

The Nature of the Lesion.

If we could see the changes which occur at the onset of a morbid process, are they different in different diseases?

Take a well-marked case of neurasthenia where a man in the prime of life begins to lose his mental capacity; his memory

fails, he loses interest in everything; he cannot bring himself to do simple things, such as the writing of a letter. We assume that his cortical cells are deranged. In what way are they altered? Is the kind of change different to that which constitutes the initial stage, say, of general paralysis? In both diseases we have reason to believe that the cause is a toxin; in general paralysis this is usually of syphilitic origin; in neurasthenia its origin is not known. If the very earliest changes in the cortical cells of the two diseases were visible, would they be like or unlike? If like, we must assume that different poisons may at first produce the same results; and then, if the changes in the one case are progressive, and lead to degeneration of the cells, which is represented by the symptoms of general paralysis, while in the case of neurasthenia they are more or less stationary, we should be at a loss for an explanation. Probably, if we found similar identity in the initial morbid changes of other diseases, we should be disposed to believe that variations in progress might be due to variations in the dose of poisons; that a case of neurasthenia, for example, which had remained stationary for some time, might, if the dose of its poison were increased, develop into one of general paralysis; in other words, that one disease might pass into another. This is a fascinating speculation, and is to some extent supported by the transitional clinical forms that are met with between well-marked types of different diseases. But, for my own part, I prefer to believe that each poison has its own point of attack, and that the earliest change of each disease has its own peculiarities, minute enough, no doubt, and still invisible to our present methods, but which, if visible and thoroughly recognised, would enable us to diagnose the condition and to foretell its probable developments.

This view receives support from the investigations of Lugaro, whom I have already quoted. He says:[2] "The study of subacute intoxications has shown us that, while the primary lesions of the nerve cells have common features, there are not wanting in them particular characters by which we can more or less

completely distinguish one intoxication from another. The alterations that result from chronic intoxications present, according to Nissl, a remarkable uniformity, both as a whole and individually. This fact, I believe, may be explained by the circumstance that the toxic action is complicated by autotoxic actions resulting from secondary disturbances of metabolism, and from alterations of the other viscera that reciprocally exercise an influence on the brain. These secondary disturbances, relatively uniform, must tend to mask the primary action, cancelling the original diversity of the picture produced by the various agents. The action of general and local infections of the nervous system has a very great analogy to that of the intoxications. This we can easily understand if we consider the greater importance of the indirect and general action exercised by the micro-organisms through their toxins in comparison with their direct and local action."

Are there any changes which immediately precede the minute ones in nerve cells which I have assumed to constitute the histological basis of the earliest symptoms in nervous diseases? The toxic material passes in the blood along the walls of a vessel; does it attack the nerve cell only, or does it first attack the delicate and active endothelial cells lining the vessel?

It is possible that some toxins may first attack the nerve cell and have their action limited to it, at least for a time, but histological evidence speaks strongly in favour of a previous, or at any rate of an associated, vascular lesion. Undoubtedly the prevalence of vascular lesions is the most striking thing in the morbid anatomy of cord and brain diseases. In all forms of myelitis, in disseminated sclerosis, and in poliomyelitis the spots of disease are closely related to the distribution of blood vessels, which may contain thrombi, have their coats thickened and their perivascular lymph sheaths crowded with round cells. These changes strongly suggest the action of some irritant on the endothelial lining of the vessel, which leads to an increased flow of lymph and leucocytes into the perivascular tissues, and thus

initiates the earliest nerve lesions. Apart, too, from visible vascular lesions, an irritant may set up spasm of muscle in the wall of an artery, for it seems probable that vasomotor spasms may play an important part in the symptomatology not only of organic disease, but also of hysteria, neurasthenia, headache, and many other functional affections.

Prognosis in Relation to Symptoms.

We have seen that the influences at work in the production of disease and its effects are manifold, for in addition to the morbid changes which occur in the part attacked, which present infinite variations owing to variations in the nature and strength of the attack and of the resistance offered to it, we have to consider the changes which may be set up at a distance from the lesion, changes which whether temporary or permanent may cause certain inhibitory or accelerating influences to be exerted on the functions of various parts of the nervous system. If, then, the influences at work and their effects are so complicated, how shall we adequately interpret the results? The only manifestations to us are symptoms, and these depend not on all, but only on some of the results of the disease. Our difficulties are still further increased by the fact that symptoms vary in different persons quite apart from the severity, distribution, and nature of the lesion. For example, with the same amount of irritation of sensory fibres the perception of pain in one person is extreme, in another very slight. Thus one has watched the course of painless intrathoracic aneurysms and of pyloric cancers, and has felt convinced that the mere locality of the lesion was not sufficient in itself to account for the absence of pain. Again, one has seen cases of cerebral tumour in which headache was but slight, and certainly far from constant.

Without stopping to find reasons for such idiosyncrasy one may bear it in mind as a partial explanation of variations in other symptoms, objective as well as subjective; thus I do not think that morbid anatomy always explains why paralysis is

profound in one person, moderate or only slight in degree in another, or why the degree of muscular spasm varies so much in affections of the upper neuron.

As an example of want of correlation between symptoms and morbid anatomy the following case of glioma of the cord is worthy of record: —

A man, aged 24, was admitted under my care at the Manchester Royal Infirmary last June, complaining of weakness of the right arm. He stated that he first noticed the weakness on waking one morning, about three months before admission, and that during the last four weeks his neck had felt stiff and sore. On examination, all the muscles of the right arm were weak and wasted; he could feebly flex the wrist and fingers, and feebly supinate and pronate the hand, but he was unable to extend the wrist, or to perform any movements at the elbow or shoulder. The power of the left arm was good, with the exception of flexion of the hand and fingers, which was feeble. As regards cutaneous sensibility he could feel the slightest touch, and everywhere could distinguish between the head and the point of a pin. Sometimes the pain produced by a pin-prick seemed to last longer than normal, and sometimes he multiplied the number of points of contact; occasionally he appeared unable to distinguish between a hot and a cold test tube when applied to the right arm. The head was inclined towards the left shoulder he was unable to move it back beyond the vertical position. He could turn his chin better towards the left than the right side; this was due to pain in the neck rather than to muscular weakness. The fifth and sixth cervical spines were tender to pressure, but only to a slight degree; and the skin of the right side of the neck was a little more tender to pressure than that of the left side. There was no hyperæsthesia elsewhere. Both knee-jerks were present; the right was feebler than normal. On June 22nd patient was shown at a meeting of the Neurological Society held in Manchester, and various opinions were expressed as to the nature of the lesion. At this time sensation was practically normal, and the neck tenderness was very slight; there was indeed no evidence that any of the cervical roots were involved. Most of those who examined the case regarded it as one of anterior poliomyelitis: one or two members of the Society suggested the possibility

of a new growth involving the cord. At the end of June weakness of the left arm became more marked, and the first dorsal interosseous muscle was distinctly wasted. A blister formed on the palmar surface of the third finger, and a little later another developed on the dorsal aspect of the middle finger. After two or three consultations with Mr. Thorburn it was decided that a growth could not be excluded, and on July 9th Mr. Thorburn performed laminectomy. No growth was found outside the dura, nor was there any indication of bone disease. On opening the dura a great deal of spinal fluid escaped, but no lesion was discovered. After the operation patient was quite comfortable, and his breathing natural. He was unable to pass water, which had to be withdrawn by the catheter. The evening temperature was 100°. His

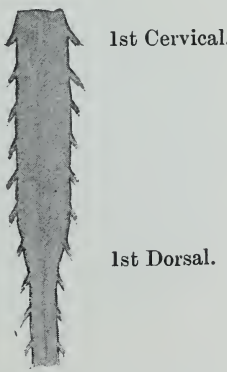

FIG. 1.—Outline of cervical cord.

condition remained favourable till the following evening, when his temperature rose to 103°, and his breathing became hurried and distressed. The left arm was now much weaker than before the operation. The retention of urine continued. On July 11th patient was decidedly worse, and almost completely paralysed. His face was flushed, and his breathing was entirely, or almost entirely, diaphragmatic. Both arms were completely paralysed; the legs could be slightly moved by a voluntary effort, but such movement amounted to little more than a twitch. A most careful examination failed to indicate any trace of anæsthesia or of hyperæsthesia. The knee-jerks were absent. The breathing became more and more embarrassed, and he died in the afternoon.

For the following pathological report I am indebted to Dr. Moore :— Body that of a tall, well-nourished, muscular man. Marked atrophy of the muscles of the right arm. The intrathoracic and abdominal organs were apparently normal. The brain also presented a healthy appearance. The cervical portion of the spinal cord was greatly enlarged in its whole extent. On section this was found to be due to the presence of an elongated ovoid mass of new growth, which extended from the second segment to the commencement of the dorsal cord (Fig. 1). At the upper and lower ends the mass of new growth gradually became thinner, and terminated in a bent cone. To the naked eye the cut surface of the tumour presented a uniform greyish, semitranslucent appearance;

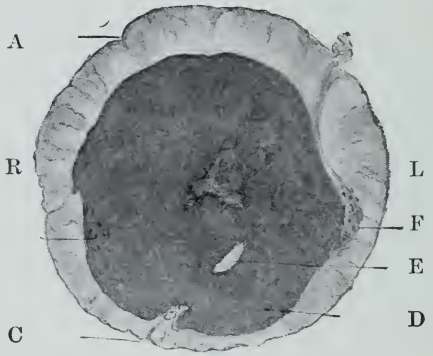

FIG. 2.—Section of cervical cord. A, posterior fissure; B, ganglion cells of anterior cornu; C, anterior fissure; D, new growth; E, central canal; F, anterior cornu.

peripherally it was invested by a thin layer of white matter. A section through the middle region of the tumour showed under the microscope that the new-formed tissue occupied the greater portion of the transverse area; it was completely invested by a narrow zone, varying in thickness, of nerve tissue. The growth approached nearer to the anterior than the posterior surface of the cord, and nearer to the right than the left side. In structure it consisted of a matrix of interlacing fine fibres containing a considerable number of cells, many of which were large and multinuclear; others were small, and obviously belonged to the neuroglia. There were some scattered capillary vessels. The new

growth was apparently a neuroglioma, and had probably originated in the tissue round the central canal. The periphery of the tumour was well defined and sharply delimited from the investing nerve tissues. On the left side the cornua—anterior and posterior—of grey matter were drawn out antero-posteriorly and compressed laterally (Fig. 2, p. 16). In structure they appeared quite normal, the large ganglion cells being unchanged. The left lateral column of white matter was compressed, but its area was probably not diminished in size and its component fibres were unaltered. The left posterior column, also altered in shape, was not much diminished in area and was not degenerated. The anterior column was greatly attenuated, and was represented by a narrow zone of fibres compressed between the bulging tumour and the pia arachnoid. On the right side of the tumour the grey matter was represented by a few scattered ganglion cells, which were situated in the outer zone of the tumour. These few cells were normal in appearance. The lateral and posterior columns, though deformed, were apparently but little altered; probably, however, there was some destruction of their fibres owing to the encroachment of the tumour.

In the next place we must remember what Dr. Hughlings Jackson has so justly emphasised—namely, that symptoms are due as much to normal physiological functional activity imperfectly applied as to the actual loss of function occasioned by the lesion; in other words, that symptoms result not only from the changes at the seat of the lesion, but also from the normal or perverted action of healthy neurons, as an indirect effect of the lesion. Thus the foot deformities met with in infantile paralysis are partly due to the unopposed action of healthy muscles, while the exaggerated movements of a tabetic patient depend to some extent on lowered tonus of the muscles through a cutting off of sensory impulses from the motor neurons. An analogous phenomenon is the muscular atrophy which follows articular inflammation, or that which occasionally attacks a hemiplegic limb. These effects probably result from inhibition of the functions of nerve cells. As another instance of inhibition may be mentioned cases of granular kidney unattended by

dropsy, in which, when an attack of hemiplegia occurs, the paralysed leg becomes œdematous.

Furthermore, we may observe that symptoms represent both active and passive or arrested phases of disease. For example, we see two cases of what are called birth palsies. The patients have reached the same age, and both exhibit spastic limbs and a certain degree of dementia. In one case the condition has been stationary for many years; in the other, convulsive attacks have occurred every week or every month since infancy, and the mental functions have gradually deteriorated. In both cases there is permanent damage to cortical cells; in the first case this is all, and the physical health and the duration of life are not seriously imperilled: certain functions are lost by the cutting off of a part of the brain, as the functions of a limb are lost by its amputation. But in the second case, living cortical cells are disordered, and the manifestations of the disorder indicate the probability of a downward course.

It is then the symptoms which testify to active phases of disease which, for purposes of prognosis, require to be carefully studied. They have a natural history of their own which calls for independent investigation, and which is not as yet adequately explained by morbid anatomy. Very often, indeed, a group of symptoms is the only part of the disease known to us. To this we give a name, and are said to have made a diagnosis. Thus to one group of symptoms we give the name of tetany, to another paralysis agitans, to a third epilepsy. In epilepsy we assume that the cells of the cerebral cortex are at fault, but in tetany and paralysis agitans we know neither the site nor the nature of the lesion. In such cases as these, accuracy of prognosis will vary with accuracy of observation in regard to symptoms. We require to have a thorough acquaintance first with types, and, secondly, with aberrant forms. In short, we ought to know the natural history of the disease as revealed to us by its symptomatology.

In these days, when the chemistry of nerve tissue and the

pathology of the neuron are so keenly investigated, we may ask: Is the same ardour evinced by clinicians in the study of symptoms. Do we accurately note day by day the variations in the symptoms of cases, say, of myelitis or of locomotor ataxy? When we have done so we have been astonished to find how frequently slight variations may be detected even when the case is to all appearances a chronic one. We talk of the influence of the mind on the body and of the body on the mind as if their mutual relationships were well understood, but do we understand the meaning of the trophic lesions so often met with in the insane, or the temporary improvements which sometimes occur in the subjects of organic disease who visit such places as Lourdes and Holywell? In one case of transverse myelitis known to me, a man who was unable to walk bathed at Holywell. After the dip he was able to walk, and the next day he walked without crutches. The improvement lasted for ten days, and then the paralysis returned, when he came under the care of Dr. Dreschfeld, at the Manchester Royal Infirmary. Such improvement is not more wonderful than the temporary improvement in insanity which follows the application of a blister to the neck. On the other hand, can we distinguish between the mental phenomena of visceral disease—for example, can we speak accurately regarding the various states of mental depression seen in stomach affections, or differentiate the psychical symptoms which occur in the later phases of lung and heart diseases.

The more closely we study symptomatology, the more we are struck by its complexity and by the necessity for greater care in making our observations and in forming our judgments. As already indicated, diseases of the nervous system may be divided into two groups, according to the presence or absence of visible morbid changes. A disease belonging to the group which is represented to us by symptoms only may have its course foretold as well as one of which the morbid anatomy is well known. A correct prognosis of any particular case of paralysis agitans is neither more difficult nor more easy to make than one of

disseminated sclerosis. Prognosis depends less on our knowledge of pathology than on the accuracy of our experience with regard to symptomatology. But sometimes we observe a group of symptoms or a single symptom which, although it may give us a clue as to the part of the nervous system affected, does not enable us to make a diagnosis in any acceptation of the word.

Of isolated symptoms, numbness is one of the most common. This subjective sensation may or may not be associated with slight anæsthesia. What is its significance?

A married lady consulted me four years ago for numbness of the left arm and hand. On examination, I found slight tenderness over the fifth cervical spine and slight relative anæsthesia down the outer side of the arm. There was no hyperæsthesia, and there were no other symptoms whatever. She was not hysterical, and there was no evidence of gout, dyspepsia, or any other possible cause. She came again to see me the other day; the symptoms were unaltered, and she said that, in spite of massage and other treatment, the numbness had been present every day during the four years; in other respects she was quite well.

I have seen several cases of numbness and slight anæsthesia, often of root distribution, sometimes in connection with dyspepsia —as in one case where the distribution was along the inner aspects of both arms, in which the symptoms passed away after a few weeks. In the case just related there is no reason to suspect serious disease, but we cannot exclude it, we cannot deny the possibility that the agent at work is a pernicious one, which in another person might have led to a disseminated myelitis or other serious disease, instead of its action being checked as in the above case. The persistence of the numbness, especially as it is a sensory symptom, is remarkable, but perhaps not more so than the persistence of some cases of neurasthenia and of other so-called functional affections.

In contrast to the above case, the following is of much interest: —

In December, 1893, a young lady consulted me for numbness of the feet and the left side of the face. Her manner was somewhat hysterical,

and I was unable to find any objective signs of disease. The numbness passed off in two or three weeks. Eighteen months later she consulted me again; she complained of much weakness, and looked ill and thin, but the only definite evidence of disease was a distinct exaggeration of the wrist-jerks and knee-jerks. This symptom made me suspect the onset of disseminated sclerosis, and the other well-marked symptoms of this malady gradually developed, and she died three years later.

In this case is the numbness to be regarded as an early symptom of the disease which ultimately declared itself in an unmistakable manner? Was it the result of exudations in the sensory path set up by the toxin of sclerosis, or was it the result of some other cause? I am inclined to take the former view, although, speaking generally, I do not think that numbness *per se* is a symptom which is commonly of much significance, for nerve tissue is often so unstable that a very slight alteration in the quantity or the quality of its blood supply may lead to interference with sensory conduction. At the same time, numbness does indicate a disorder of the sensory path, and therefore its presence suggests the necessity of making repeated careful examinations of the patient who suffers from it.

The first case of persistent numbness shows that a definite lesion of the fifth cervical root has existed for four years. Obviously the lesion is a very slight one; it may be the result of the constant action of some poison which shows a preference for that particular region, for of the curious ways in which poisons locate themselves there appears to be no end; while, owing to our imperfect methods of producing elimination, the local toxic effects may persist indefinitely. Indeed, it seems reasonable to suppose that almost any variety of cell or fibre may be selected by a poison as its seat of attack. Thus the poison of tetanus selects the motor nucleus of the fifth cranial nerve, nicotine picks out the optic nerves, lead some of the branches of the musculo-spinal nerves, while the toxin of influenza may attack almost any part of the nervous system. Reference to our knowledge of influenza would alone justify the assumption

I have made regarding the unlimited modes of selection exhibited by poisons in different cases.

Paralysis of some of the eye muscles may be mentioned as another isolated symptom that is often difficult to understand. Some cases are met with apart from syphilis or influenza, or other ascertainable cause.

Last February, a man, aged 37, consulted me, through the kind recommendation of Dr. Emrys Jones, for double vision and general debility. He said the symptom, "seeing double," was first noticed on getting up one morning, about a week ago; it was preceded by numbness of the fingers for two or three days. I found complete paralysis of the right external rectus, partial paralysis of the left internal rectus, and slight impairment of the movements of the right facial muscles; no other symptoms were present. The man was a clerk, and had felt over-tired for some time. No other morbid antecedent than overwork could be discovered. I saw him again in March and in April, and on each occasion the symptoms were less marked. In May, that is three months from the onset of his disability, no paralysis could be detected. The treatment consisted in the administration of strychnine and potassium iodide, and in rest from work.

The significance of a numbness or a limited paralysis is hard to determine, and a cautious prognosis must of necessity be given. Even if we knew the exact nature of the toxin we could not foretell the issue with certainty. Probably in a large number of what are called functional paralyses the minute lesions are quite different from those which constitute the initial stage of a serious disease such as disseminated sclerosis; but we must not regard complete recovery as a differential test; surely it is reasonable to believe that the minute initial changes of a serious disease may be removed and that no future developments will take place. I think that evidence in support of such a belief is afforded as we shall presently mention by a study of the course of serious organic disease. I would contend that the constant use of the term "functional" has hindered the advance of knowledge. Its implication that the changes at present

invisible to us are of different nature to those at the onset of serious disease has alone sufficed to limit our view and to prevent our thoughts taking the direction just indicated.

Similar remarks might be made regarding the use of the word "hysteria"; a discussion on this subject, however, is somewhat outside my present topic. It must suffice to remind you of the investigations of Buzzard, Bastian, and others, which have done so much to narrow the boundaries of hysteria; and to state my belief that increasing knowledge of pathology will tend to reduce its limits still further. Prolonged vascular spasm or some other lesion must underlie a profound anæsthesia or a contraction of the visual fields. What is meant by calling these phenomena hysterical? In some cases they persist for years, even throughout life, and when they disappear have we adequate knowledge of the subsequent nervous history of the patient? With regard to motor phenomena, such an authority as Charcot has stated that persistent hysterical contractures, after lasting for many years, may be attended with structural changes in the spinal cord; in one case he found a lateral sclerosis, which apparently he regards as a direct outcome of changes started by the hysterical contracture. I find it much easier to believe that from the very first there were minute definite changes to which any hysterical or psychical manifestations were secondary. Commonly enough, such manifestations are met with in association with and frequently overshadowing symptoms indicating organic disease. They are often misleading, and tend to make us overlook the significance of a definitive objective sign such as paralysis of a group of muscles. In my experience it is rare to meet with psychical paralysis, and when it occurs it is weakness of a complicated movement rather than of individual muscles. Thus the power to stand or walk may be lost when the movements of the legs in bed are normally performed. We are told that such a patient is not shamming, but is suffering from a genuine disease, hysteria; it is always difficult, however, to exclude the absence of real effort on the part of the patient.

I will now briefly relate the clinical histories of three remarkable cases of recovery from symptoms which indicated serious disease. In the first case hysterical manifestations were present, in the other cases they were absent.

The first patient, a girl, aged 22, was under my care at the Manchester Royal Infirmary from October, 1893, to May, 1894. There was a history of headache, of impaired vision, and of occasional partial losses of consciousness. On admission she was dull, apathetic, and hysterical. There was partial paralysis of the right arm and leg, and at times of the right side of the face. Optic neuritis was well marked; she suffered from constant headache, and pain was caused by pressing on the occiput and neck. At first cutaneous sensibility was normal, but at a later period there was partial anæsthesia down the left side; then paralysis of the right external rectus was noticed. Subsequently the hemianæsthesia disappeared and the left limbs became weak, but they were not so paralysed as the right limbs, which at one time seemed to be deprived of all power of voluntary movement. Optic atrophy succeeded the neuritis, and the girl became absolutely blind with the left eye and partially blind with the right eye. During this time the right knee-jerk was exaggerated and the left one very feeble; there was no ankle clonus. In December, that is three months after admission, double ptosis developed. In January the ptosis had disappeared as well as the paralysis of the right external rectus. In February she passed every night in a semiconscious, delirious state. In March she was able to walk with assistance in a feeble manner. On leaving the hospital in May she went to stay with friends in London. Towards the end of 1894 Dr. Beevor wrote to me saying that she was an inmate of the National Hospital in Queen Square. In reply to his inquiries I gave him the history of the case, and said that if it had not been for the optic neuritis and the affection of the right sixth nerve I should have been inclined to regard the case as a so-called functional one. A few months later he wrote again, saying that her symptoms had become worse; vomiting and headache were severe, there was marked staggering in walking, double ptosis was present, and there was anæsthesia down the right side.

Dr. Beevor thought there was a tumour in the neighbourhood of the left occipital lobe, and, after a consultation with Mr. Ballance, it was

decided to trephine. Mr. Ballance operated, and found nothing abnormal. The patient made a good recovery from the operation; the headache and vomiting ceased; the ptosis, however, and a loss of conjugate movement of both eyes to the left persisted, as also did the right hemianæsthesia. A few weeks later she became maniacal. But what was most interesting, wrote Dr. Beevor, her ptosis, conjugate paralysis, and hemianæsthesia all disappeared, and her sight returned, so that she could read small print. "I am now inclined to agree with you that, except for the optic neuritis followed by atrophy, the case looks very like a functional one." The girl was sent to Bethlem Hospital. Some eighteen months later I was surprised to receive a well-written letter from her, in which she stated that she was quite well with one exception, namely, that her eyes became painful after reading a few words.

Time will not permit me to comment on this remarkable case, but I would repeat that definite objective signs of brain disease were observed both in Manchester and in London, that they entirely passed away, and that the patient regained her health, and was able to resume her occupation.

The second case, which I saw with Dr. Robinson, of Dunsear, in February, 1897, was one of spastic paralysis in a young woman, aged 22. She had suffered from numbness and weakness in the legs for three months before I saw her. Her gait was feeble and spastic in character. The flexor movements at hip, knee, and ankle were weaker than normal; the extensor movements were fairly strong. The legs were very rigid; the knee-jerk was much exaggerated, and there was well-marked ankle clonus. The right abdominal reflexes were present, the left could not be obtained; the plantar reflex was absent. The cutaneous sensibility was unimpaired; micturition was somewhat delayed.

After a full consideration of the case, I concluded that it was not one of hysteria, and that the diagnosis rested between a dorsal myelitis and disseminated sclerosis, the latter being by far the most likely. The patient made a good recovery, and Dr. Robinson informed me the other day that she is still quite well.

Is this an instance of mistaken diagnosis or one of recovery

from serious disease? Let me insist on the character of the ankle clonus. It was well marked, and quite different from the feeble, loose variety met with in hysterical subjects, and, with experience of other similar cases, I am convinced that paralysis with a true foot clonus, apart from hysterical contracture, is occasionally recovered from. Dr. Buzzard has recorded cases in which apparent recovery from disseminated sclerosis has lasted four or five years; hence, it is not impossible that the patient referred to, who has been free from symptoms for nearly four years, is not entirely out of danger. As to the absence of the plantar reflex, I have observed its occurrence in other cases of disseminated sclerosis. In one case which I reported some years ago the reflex was absent till towards the termination of the disease, and, although I recognise the importance of the extensor response as an indication of affections of the upper neuron, I do not regard it as a pathognomonic sign.

The third case was one of atrophic paralysis affecting a girl aged 9, whom I examined in October, 1895. Both feet were dropped, and all the muscles on the front of the legs were paralysed and wasted. The knee-jerks were absent; sensation was normal; there was no affection of the bladder or the rectum. A careful examination of the spine revealed nothing abnormal. The diagnosis seemed to rest between acute anterior poliomyelitis and a motor type of multiple neuritis. I considered the former diagnosis the more probable of the two, and gave a cautious prognosis, and prescribed massage and other local stimulating treatment. In a year's time the muscles had almost completely recovered their normal bulk and power. In response to a letter she came to see me last August, just six years from the onset of the disease. The girl had a robust appearance, and her legs were quite healthy and strong. She told me that occasionally she walked rather clumsily, and that she was subject to cold feet. The right knee-jerk was normal, the left was a little exaggerated.

These symptoms seemed to support the original diagnosis, and I am inclined to regard the case as an instance of recovery from acute anterior poliomyelitis.

I will now leave cases of doubtful nature in order to have time to consider the course of diseases in which the diagnosis is certain, and where there can be no doubt that the symptoms are associated with obvious structural changes.

Some time ago I saw a child, aged four years, in the later stages of tuberculous meningitis, who suddenly passed from a state of deep coma to apparent convalescence; for a few hours he was bright, spoke to his mother, and played with his toys, and then relapsed into fatal unconsciousness. Such fallacious improvement in this disease is well known, and would not deceive the skilled observer. It is worth noting, because it seems to indicate that the freely circulating toxin which produces the coma may have its effects temporarily arrested by an antitoxin, or in some other way, and taken in conjunction with exceptional cases of recovery from tuberculous meningitis, it gives rise to a hope that some day an antitoxin may be discovered which will counteract the effects of the poison.

The next case I would refer to was seen by Drs. Dreschfeld and Little, and was diagnosed acute disseminated myelitis after measles.

The patient was a young lady, aged 18, who, the day after taking a cold bath, broke out with the rash of measles. Whilst recovering from the attack of measles she complained of intense headache, of weakness of the legs, and of pain in the back. It was found that she had optic neuritis, and in a few days she became totally blind. The blindness was followed by paralysis, first of the legs and then of the arms; their cutaneous sensibility was also markedly impaired. There was retention of urine, with occasional incontinence. Within a month from the onset of measles all four limbs were completely paralysed. A fortnight later motor power began to return, and in about four months the girl was quite well.

A study of the course of chronic nervous diseases such as disseminated sclerosis, locomotor ataxy, general paralysis, and myelitis is also full of interest in connection with our present subject. It teaches us that the downward progress, which un-

fortunately characterises the majority of cases, is by no means made by a constant succession of regular steps. On the contrary, it presents a most irregular course, of which the variations are infinite both in kind and in time of succession. Arrest of a chronic disease may occur at any stage; and while, as a rule, it is only temporary, it may be permanent. We are impressed not only with the rare complete recoveries which may occur, but with the stationary periods, with the periods of marked improvement, and with the disappearance of individual symptoms, and their replacement sooner or later by others of the same or different kind. These points have been so ably illustrated by Dr. Buzzard in his studies on disseminated sclerosis, that I need not further refer to that disease except to state that I could give examples from cases of my own of the various phases he describes, and of the risks to diagnosis from the presence of hysterical manifestations to which he draws such just attention.

The clinical histories of locomotor ataxy and general paralysis are prolific in instances of arrested progress and of alternating periods of improvement and breakdown. Sometimes, as in the following case, prolonged improvement or apparent recovery may be followed by symptoms almost malignant in their severity and rapidity of progress.

The case was that of a gentleman, aged 27, who consulted me in August, 1891, and was subsequently seen by Sir Thomas Barlow. When first seen he had definite ataxia, shooting pains in the legs, delayed sensation, delayed micturition, and the knee-jerk was absent. Some of these symptoms subsided, especially the bladder disturbance. He went to Aix-la-Chapelle, and was much benefited by the treatment. In September, 1892, he paid a second visit to Aix, and there was still further improvement. He was married in December, and continued to steadily improve. In May, 1893, that is nearly two years after I first saw him, he wrote as follows: "I have regained my power of work, and no longer experience extreme fatigue or distressing symptoms of any kind. My gait in walking is practically normal, and I can daily walk

any distance with as little exertion as before the complaint overtook me. The only remaining symptoms I notice are anæsthesia in the toes and some clumsiness in running movements, which, however, is much less when the muscles are fresh than when they are tired. The knee-jerk is still absent."

A few months later, however, fresh symptoms developed—namely, œdema of the ankles and some small perforating ulcers. He was sent to undergo Erb's treatment at Heidelberg. This did not answer at all; he had a succession of bad arthropathies affecting the hips, knees, and shoulders. A little later symptoms of general paralysis set in rather abruptly, and he was sent to an asylum.

Additional interest is attached to this case, owing to its etiology. It is certain that the patient had not acquired syphilis in the ordinary way; he had a protracted illness after vaccination in infancy, which the medical man who vaccinated him regarded as due to inoculated syphilis.

Similar varying phases characterise the progress of general paralysis.

Thus a medical man suffered from well-marked symptoms of this disease, and his friends were advised to sell his practice. They did so. Subsequently he recovered to such an extent that he appeared to be quite well. He married, and remained in what seemed to be good health for about a year; then he suddenly broke down with aggravated symptoms of general paralysis, and died shortly after.

What is the pathology of these variations in progress? I would submit that they support the view of a general toxic condition rather than that which has recently been so ably advocated by Dr. Mott—namely, that in tabes and general paralysis the syphilitic poison has so lowered the vitality of nerve elements that they undergo a primary and progressive decay. Let me again observe that the course of these diseases is not steadily progressive, that a subsidence of symptoms is followed by fresh outbursts, and that apparent recovery is often suddenly interrupted by the development of acute symptoms in various parts of the body. Such fluctuations remind one in a way of the

temperature chart of a prolonged case of enteric fever, in which at irregular intervals a series of high temperatures alternates with a series of low ones, the high curve corresponding to a fresh development of toxins, the low curve corresponding to abatement of their action. It is difficult to understand how the ups and downs, which are such marked features in the clinical history of chronic nervous diseases, can be explained on the hypothesis of primary progressive degeneration of neurons owing to exhaustion of their specific vital energy, and apart from the direct action of toxins circulating in the blood.

Prognosis in Relation to Treatment.

If I am right in assuming that a poison is the most common exciting cause of diseases of the nervous system, prognosis will vary with knowledge of the proper treatment for elimination of the poison, and of the effects produced by it. But in most cases we know neither the nature of the poison nor the manner in which it enters the circulation, hence treatment is purely empirical and often fails. When we do know what the poison is, and how it is introduced into the blood, as in the case of lead, we can stop any further introduction of the poison, and then try to eliminate what is already present. Our methods of elimination, however, are still too crude for the purpose. We may employ massage and baths, administer purgatives and alteratives, and place the patient under the best hygienic conditions, often without producing any immediate result, witness the persistence of some cases of peripheral neuritis or of neuræsthesia in spite of the most energetic treatment, and our inability to stop the progress of an early myelitis.

In addition to remedies for the elimination of poisons we want others to aid us in counteracting their effects, and here we must hope for fresh discoveries regarding the effects of glandular extracts and the nature of toxins and their antitoxins.

In this connection the influence of one disease upon another is worthy of renewed investigation. Two examples may be

mentioned:—A boy with whooping-cough was attacked with most severe urticaria; the whooping-cough quickly subsided. A man, whilst suffering from severe neuralgia on the right side of the neck, had an attack of bronchitis. Its onset was associated with a sudden disappearance of the neuralgia.

The possibility that a second attack of the same disease may have a beneficial effect on the symptoms left by a first attack is suggested by a case which was recently under the care of Dr. Dreschfeld. A man whilst suffering from influenza began to show symptoms of grave mental disturbance. He talked incoherently, was dull and apathetic, and passed his excreta into the bed. In a few weeks he was sufficiently recovered to take a holiday. Two months later he resumed his business, but his mental vigour was much less than before his illness. Six months after the first attack he had another attack of influenza, and was very much afraid that his former symptoms would return: but to the astonishment of himself, his friends, and his doctor, he made a rapid recovery, lost all his old symptoms, and regained complete health both mental and physical.

We have, further, to study the influence of one part of the nervous system upon another part. Thus, a knowledge of the value of sensory impulses in maintaining the proper nutrition of motor neurons affords an explanation of the beneficial effects of massage, passive movements, and galvanism as stimulants to the regeneration of damaged nerve tissue. We also recognise the important influence that cheerful surroundings, sunlight, and other psychical stimulants may have upon morbid processes, and we admit the possibility that a powerful emotion may initiate a change for the better, either by stimulating the metabolism of diseased tissue or by opening up fresh paths for the transmission of motor or sensory impulses. As Dr. Mott points out: "Consciously and unconsciously, a continuous stream of impulses is pouring into the nervous system from without by the sensory channels, which are the avenues of experience and intelligence,

and our bodily and psychical life depends upon the existence of such stimuli."

A consideration of these and of other facts which, as I have indicated, may be derived from a study of pathology and of the history of symptoms, gives us hope for the future. It suggests that further investigations—clinical, pathological, and chemical—will do much to lighten the gloom which at present surrounds the prognosis of so many disorders of the nervous system.

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